Maximal Oxygen Uptake and Severity of Disease in Lymphangioleiomyomatosis

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Lymphangioleiomyomatosis (LAM), a disease that occurs primarily in women, is characterized by cystic lung lesions causing respiratory failure, which may require lung transplantation. Lung diffusion ($D_{L_{CO}}$) and/or FEV_1 are decreased, but frequently not in parallel with each other. Because cardiopulmonary exercise testing (CPET) provides information that is not obtainable from resting cardiopulmonary tests, we performed CPET in 217 LAM patients and correlated exercise data with clinical markers of severity, computed tomography scans, lung function, and histology. $\dot{V}O_2$max was decreased in 162 patients, of whom 28 did not reach anaerobic threshold; 29 had low oxygen uptake at anaerobic threshold, and 54 developed hypoxemia. Hypoxemia occurred even in patients with near normal $D_{L_{CO}}$ and FEV_1. $\dot{V}O_2$max decreased with an increasing score of histologic LAM severity and was correlated with computed tomography scans, the use of oxygen, and resting Pa_{O_2}. $D_{L_{CO}}$ and FEV_1, however, were the only significant predictors of $\dot{V}O_2$max. We conclude that CPET uncovers the presence of exercise-induced hypoxemia and assists in grading the severity of disease and determining supplemental oxygen requirements in patients with LAM.

Keywords: interstitial lung disease; maximal oxygen uptake; diffusion capacity; computed tomography scan; lung histology

Lymphangioleiomyomatosis (LAM), a disease affecting primarily women, is characterized by progressive cystic lung lesions, recurrent pneumothoraces, chylous effusions, lymphatic tumors, and angiomyolipomas (1–3). The clinical course of LAM is highly variable. In some patients, the disease remains quiescent, and pulmonary function tests show only a slow decline in function. In others, a loss of function is rapid, and the time from the first symptoms to onset of respiratory failure and lung transplantation may be only a few years. Pulmonary function abnormalities in LAM consist primarily of impaired diffusion capacity ($D_{L_{CO}}$) and FEV_1 (1–4). However, abnormalities of $D_{L_{CO}}$ and FEV_1, that is, severity of impairment and rates of decline, do not parallel each other (4), which raises the question of how the two tests should be employed to grade the severity and progression of disease. Although the functional limitation in some patients appears to be related to ventilatory problems caused by airflow obstruction, other patients have almost exclusively an impairment in $D_{L_{CO}}$ with well-preserved flow rates. In patients with LAM, objective evidence of exercise limitation, along with exercise-induced hypoxemia, has led us to question whether standard pulmonary function tests are an adequate measure of disease severity.

Because cardiopulmonary exercise testing (CPET) evaluates all components of exercise responses and provides information that is not available from tests of pulmonary and cardiac function at rest (5), it may be a preferable method for grading the severity of disease in LAM. Based on this hypothesis, the principal aim of our study was to determine the causes of exercise intolerance in LAM and use the CPET data to grade the severity of disease. To accomplish these objectives, we compared cardiopulmonary exercise data with high-resolution lung computed tomography (CT) scans, pulmonary function tests, lung histology, and clinical markers of disease severity, in a large population of patients with LAM. Some of the results of these studies have been previously reported in the form of abstracts (6, 7).

METHODS

Study Population

The study population comprised 294 patients referred to National Institutes of Health for participation in an LAM protocol (NHLBI Protocol 95-H-0186) approved by the Institutional Review Board of the National Heart, Lung, and Blood Institute. All subjects gave informed consent before enrollment. The diagnosis of LAM was made by tissue biopsy in 170 patients and in the remainder by clinical and roentgenographic data (1–4). After exclusions because of death (n = 7), transplantation (n = 20), recent surgery (n = 3), joint disease (n = 4), cardiac disease (n = 3), and missed appointments (n = 40), data for analysis were available from 217 patients. One patient who participated in the study died subsequently from complications of abdominal surgery.

Pulmonary Function Tests

Lung volumes, flow rates, and $D_{L_{CO}}$ were measured using a computerized system (Master Screen PFT; Erich Jaeger, Würzburg, Germany), according to American Thoracic Society recommendations (8, 9). Percentages of predicted normal values were derived from standard equations (10–12).

Cardiopulmonary Exercise Tests

Patients were exercised on a bicycle ergometer or treadmill and a computerized metabolic cart (Vmax 229 Cardiopulmonary Exercise System; Sensormedics, Yorba Linda, CA) using standard incremental protocols (5, 13). Sa_{O_2} was measured using a pulse oximeter (Nellcor Puritan Bennett, model 295). Tests were stopped when the patient reached an oxygen uptake plateau, when Sa_{O_2} fell below 88%, or when the patient became exhausted. The following variables were measured: work rate (watts), $\dot{V}O_2$max, heart rate, oxygen pulse ($\dot{V}O_2$/heart rate), blood pressure, $\dot{V}E$, respiratory rate, tidal volume, respiratory gas exchange ratio, and ventilatory equivalent for CO_2 at anaerobic threshold (AT). Breathing reserve was calculated as MVV-$\dot{V}E$/MVV $\times$ 100 where MVV is the maximal voluntary ventilation (5, 13). MVV was estimated as $FEV_1 \times 40$. AT was determined by the dual-methods approach (5, 13). $\dot{V}O_2$max was defined as the highest oxygen uptake observed during any 30-second measurement period. Oxygen-dependent patients (n = 31) were exercised while breathing from a 30-L bag filled with a gas mixture containing oxygen at concentrations set by a blender fed by compressed

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air and oxygen tanks. Tests were supervised by a physician. Predicted values for $\dot{V}O_2$max were calculated from standard equations (14) with a correction for body weight (13). For patients exercised on treadmill, predicted $\dot{V}O_2$max was obtained by multiplying ergocycle values by 1.11 (13). $\dot{V}O_2$max values below 85% of predicted and a decline in Sa_{O_2} of 4% or more were considered abnormal (5).

High-resolution CT scans of the lungs

The grade of severity of disease was determined from high-resolution CT scans, as previously reported (15). The extent of involvement of the lungs was graded as follows: grade 0, no involvement; grade 1, less than 30% involved; grade 2, from 30 to 60% involved; and grade 3, more than 60% involved.

Histology

An LAM histology score (LHS), based on the extent of replacement of lung tissue by cystic lesions and infiltration by LAM cells, was determined using open lung biopsy specimens and was scored as follows: LHS-1 = less than 25%, LHS-2 = 25 to 50%, and LHS-3 = more than 50% (16).

Statistical Methods

To determine the best predictors of $\dot{V}O_2$max, we first estimated the correlation coefficient between $\dot{V}O_2$max and explanatory variables, including duration of disease, oxygen therapy requirements (no oxygen, oxygen during physical activities, and continuous oxygen therapy), grade of CT scan abnormality, resting Pa_{O_2}, and pulmonary function tests, to quantify any linear relationship between $\dot{V}O_2$max and any of these variables. Then, using a stepwise procedure, we conducted a multivariate regression analysis with $\dot{V}O_2$max as the dependent variable and all the independent variables found to be statistically significant at a 0.1 level in the univariate analysis.

To determine whether exercise capacity correlated with a measure of disease severity that was independent of pulmonary function tests, we defined disease severity scores based on CT scan grade: a severity score was 1, 2, or 3 if the CT scan grade was 1, 2, or 3. Because 31 of the CT scan grade 3 patients were receiving continuous supplemental oxygen, we defined an additional severity score of 4 for these patients. Then we used a one-way analysis of variance with a Bonferroni adjustment to compare the four severity groups. Analysis of variance was also used to compare other patient groups.

Unpaired Student's *t* test was employed to compare exercise and lung function data in patients exercised on room air with those exercised on supplemental oxygen and in patients with LHS of 1 with those with LHS of 2. All reported p values are two sided. Data are shown as mean ± SEM.

RESULTS

Population Characteristics and Exercise-limiting Symptoms

The mean age of the 217 patients at the time of testing was 45.0 ± 0.6 years (range of 19 to 77) and the time from diagnosis was 5.7 ± 0.3 years (range of 8 months to 22 years). Two patients were smokers (25.2 ± 2.7 pack-years), and 24 were ex-smokers (13.8 ± 1.9 pack-years).

Dyspnea was the major exercise-limiting symptom (40%), followed by leg fatigue (28%), severe hypoxemia (11%), and a combination of dyspnea and leg fatigue (7%). Three patients stopped because of dizziness and three more because of abdominal pain, whereas 14 reached a $\dot{V}O_2$max plateau. The remaining patients stopped because of general fatigue.

Exercise and Pulmonary Function Data

Table 1 shows CPET and pulmonary function data for all patients. $\dot{V}O_2$max (1,187 ± 29 ml/min), $D_{L_{CO}}$ (15.3 ± 0.4 ml/min/mm Hg), FEV_1 (2.01 ± 0.05 L), and FEV_1/FVC ratio (63.6 ± 1.1%) were decreased.

The patients on continuous oxygen therapy who were exercised while breathing supplemental oxygen were significantly older and had significantly lower $\dot{V}O_2$max, oxygen pulse, breathing reserve, $D_{L_{CO}}$, FEV_1, and resting Pa_{O_2} than patients exercised on room air (Table 2). In addition, they had a significantly greater ventilatory equivalent for CO_2 ratio at AT than patients not on continuous oxygen (Table 2).

TABLE 1. PULMONARY FUNCTION AND EXERCISE DATA IN 217 PATIENTS WITH LYMPHANGIOLEIOMYOMATOSIS

	Actual Value	Percentage Predicted
TLC	4.93 ± 0.06	95.2 ± 0.9
FRC	2.76 ± 0.04	97.9 ± 1.5
RV	1.79 ± 0.03	103.7 ± 2.0
RV/TLC	36.2 ± 0.5	
FVC	3.12 ± 0.04	89.7 ± 1.2
FEV_1	2.01 ± 0.05	75.5 ± 1.7
FEV_1/FVC	63.6 ± 1.1	
$D_{L_{CO}}$	15.3 ± 0.3	73.5 ± 1.8
$D_{L_{CO}}$/VA	3.5 ± 0.08	88.6 ± 2.0
Work rate	109.0 ± 2.8	88.8 ± 2.1
$\dot{V}O_2$max	1,186 ± 29	71.5 ± 1.7
HR max	151.4 ± 1.3	86.9 ± 0.7
$\dot{V}O_2$/HR max	7.7 ± 0.1	80.3 ± 1.6
BR	30.7 ± 1.3	
RER-AT	0.99 ± 0.002	
$\dot{V}E/\dot{V}CO_2$-AT	38.1 ± 0.6	
Pa_{O_2} (rest)	81 ± 1	

Definition of abbreviations: BR = breathing reserve (%); $D_{L_{CO}}$ = diffusion capacity for carbon monoxide (ml/minute/mm Hg); $D_{L_{CO}}$/VA = ratio of $D_{L_{CO}}$ to alveolar volume (ml/minute/mm Hg/L); HR max = heart rate at peak exercise; RER-AT = respiratory equivalent ratio at anaerobic threshold; RV = residual volume (L); RV/TLC = ratio between RV and TLC (percentage); TLC = total lung capacity (L); $\dot{V}E/\dot{V}CO_2$-AT = ventilatory equivalent for CO_2 at AT; $\dot{V}O_2$max = maximal oxygen uptake (ml/min); $\dot{V}O_2$/HR max = oxygen pulse (ml/beat/minute).

Data are means ± SEM.

CPET Abnormalities

Multiple abnormalities of ventilatory, gas exchange, and cardiovascular responses to exercise were observed in our patients. One hundred sixty-two of the 217 patients (75%) had low $\dot{V}O_2$max. Among these patients, 28 (17%) failed to reach AT and 29 (18%) reached AT at an oxygen uptake of less than 40% VO_2max predicted. Of the 162 patients, 98 (60%) showed evidence of inefficient gas exchange, of whom 54 (33%) developed hypoxemia; 114 of the 162 patients (70%) had abnormal cardiovascular responses, of which 39 (24%) appeared to be limited by low heart rate reserve and 24 (15%) by low breathing reserve. Twenty-eight patients were limited by symptoms that could not be directly attributed to cardiorespiratory limitation.

Ten of 24 patients (41%) with $D_{L_{CO}}$ between 60 and 70% predicted and 7 of 29 patients (21%) with $D_{L_{CO}}$ between 70 and 80% predicted, exercised breathing room air, experienced exercise-induced hypoxemia. Of 69 patients with $D_{L_{CO}}$ and FEV_1 of 80% or more predicted exercised on room air, 7 (10%) had exercise-induced hypoxemia. $D_{L_{CO}}$ was the single best predictor of exercise-induced hypoxemia ($r = 0.550$, $p < 0.0001$) (Figure 1).

Relationship between $\dot{V}O_2$max and Clinical Markers of Disease Severity

One hundred twenty five of the 217 patients did not use supplemental oxygen. Sixty one used oxygen during physical activities, and 31 used oxygen continuously. There were significant differences among these groups of patients. As seen in Figure 2, $\dot{V}O_2$max in patients who did not use oxygen (1,360 ± 34 ml/min, 20.4 ml/kg/min, 80.9 ± 1.9% predicted) was significantly greater than in patients who used oxygen during physical activities (1,041 ± 50 ml/min, 14.9 ml/kg/min, 63.3 ± 2.6% predicted) and patients on chronic

TABLE 2. EXERCISE PHYSIOLOGY AND LUNG FUNCTION IN TWO GROUPS OF PATIENTS WITH LYMPHANGIOLEIOMYOMATOSIS EXERCISED BREATHING AIR OR SUPPLEMENTAL OXYGEN*

	Room Air	Oxygen
Number of patients	186	31
Age	44.1 ± 0.6 (19, 67)	50.9 ± 1.7 (35, 77)†
FEV_1	2.18 ± 0.05 (0.59, 3.75)	1.02 ± 0.06 (0.47, 1.83)†
FEV_1, %	81.2 ± 1.6 (23, 132)	41.7 ± 2.6 (21, 69)†
FEV_1/FVC	67.6 ± 1.0 (25, 96)	39.7 ± 2.0 (21, 74)†
D_{LCO}	16.7 ± 0.3 (7.2, 29.0)	7.4 ± 0.3 (3.9, 10.7)†
D_{LCO}, %	79.5 ± 1.7 (33, 128)	37.1 ± 1.6 (21, 54)†
D_{LCO}/VA	3.77 ± 0.07 (1.5, 6.4)	1.90 ± 0.08 (1.03, 3.96)†
D_{LCO}/VA, %	95.2 ± 1.9 (37, 175)	48.8 ± 2.2 (23, 73)†
Work rate	115.6 ± 2.7 (24, 218)	62.2 ± 4.6 (24, 104)†
Work rate, %	94.2 ± 2.2 (18, 192)	56.8 ± 3.9 (27, 105)†
HR max	155.3 ± 1.3 (105, 200)	128.2 ± 3.0 (84, 163)†
HR max, %	88.7 ± 0.7 (61, 107)	75.9 ± 1.7 (52, 98)†
$\dot{V}O_2$max	1,256 ± 30 (406, 2,446)	768 ± 46 (283, 1,147)†
$\dot{V}O_2$max, %	75.1 ± 1.6 (22, 172)	49.8 ± 2.7 (20, 81)†
$\dot{V}O_2$/HR max	8.03 ± 0.17 (2.9, 14.6)	6.0 ± 0.37 (2.2, 10.5)†
$\dot{V}O_2$/HR, %	83.1 ± 1.7 (29, 182)	63.7 ± 3.5 (30, 112)†
$\dot{V}E$max	55.9 ± 1.2 (20, 103)	32.7 ± 2.2 (12.2, 60.3)†
BR	32.4 ± 1.4 (−36, 70)	20.1 ± 2.8 (−22, 55)†
$\dot{V}E/\dot{V}CO_2$-AT	37.9 ± 0.6 (24, 59)	47.3 ± 2.6 (30, 61)†
RER-AT	0.99 ± 0.002 (0.86, 1.0)	0.99 ± 0.005 (0.87,1.0)
FI_{O_2}	0.209	0.34 ± 0.06 (0.27, 0.42)
Pa_{O_2}, rest	84 ± 1	63 ± 2†
$^{Sa}{}_{O_2}$, rest	97.1 ± 0.2 (88, 100)	98.9 ± 0.2 (95, 100)†
Sa_{O_2}, peak exercise	94.3 ± 0.3 (83, 100)	97.3 ± 0.5 (88, 100)†
Δ Sa_{O_2}	−2.8 ± 0.2 (−13, 1)	−1.6 ± 0.4 (−8, −1)†

Definition of abbreviations: BR = breathing reserve (%); D_{LCO} = diffusion capacity for carbon monoxide (ml/minute/mm Hg); D_{LCO}/VA = ratio of D_{LCO} to alveolar volume (ml/minute/mm Hg/L); HR max = heart rate at peak exercise; RER-AT = respiratory equivalent ratio at anaerobic threshold; $\dot{V}E$max = minute ventilation at peak exercise; $\dot{V}E/\dot{V}CO_2$-AT = ventilatory equivalent for CO_2 at AT; $\dot{V}O_2$max = maximal oxygen uptake (ml/min); $\dot{V}O_2$/HR max = oxygen pulse (ml/beat/minute); Δ Sa_{O_2} = change in Sa_{O_2} with exercise (%).

* Data are means ± SEM. Ranges are shown within parentheses.

† Significantly different by unpaired *t* test ($p < 0.001$) from patients exercised breathing room air.

oxygen therapy (768 ± 46 ml/min, 10.9 ml/kg/min, 49.8 ± 2.7% predicted). D_{LCO} and FEV_1 were also significantly higher in patients who did not use oxygen (18.4 ± 0.4 ml/min/mm Hg, 87.7 ± 1.9% predicted, and 2.32 ± 0.05 L, 85.7 ± 1.8% predicted, respectively) than in patients who used oxygen during physical activities (13.2 ± 0.5 ml/min/mm Hg, 63.8 ± 2.3% predicted and 1.88 ± 0.08 L, 71.9 ± 3.2% predicted, respectively) and patients on chronic oxygen therapy (7.4 ± 0.3 ml/min/mm Hg, 37.1 ± 1.6% predicted and 1.02 ± 0.06 L, 41.7 ± 2.6% predicted, respectively) (Figure 2).

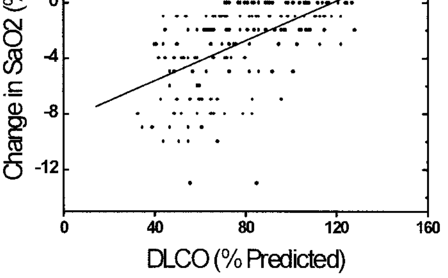

Figure 1. Correlation between lung diffusion (D_{LCO}) and change in oxygen saturation at peak exercise. D_{LCO} is shown as the percentage predicted of the normal value and change in Sa_{O_2} in percentage saturation.

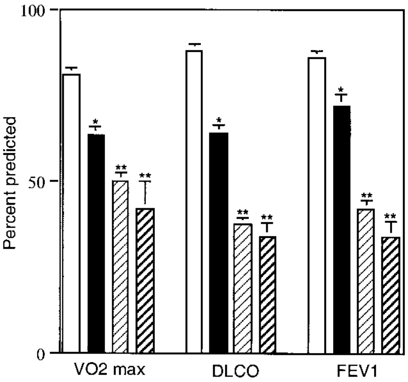

Figure 2. $\dot{V}O_2$max, D_{LCO}, and FEV_1, in patients who never used supplemental oxygen (*white bars*), patients who used supplemental oxygen during physical activities (*black bars*), patients using supplemental oxygen continuously (*thin cross-hatched bars*), and four patients just before undergoing lung transplantation (*thick cross-hatched bars*). $\dot{V}O_2$max, D_{LCO}, and FEV_1 are shown as percentage predicted values. *Significantly different by analysis of variance ($p < 0.001$) from patients not receiving supplemental oxygen. **Significantly different ($p < 0.001$) from patients not receiving supplemental oxygen and patients using supplemental oxygen only during exercise.

Four of the 217 patients underwent lung transplantation. CPET and pulmonary function tests performed before transplantation showed a $\dot{V}O_2$max of 712 ± 140 ml/min (10.5 ml/kg/min, 41.7 ± 8.1% predicted), D_{LCO} of 7.3 ± 0.9 ml/min/mm Hg (34.0 ± 3.9% predicted) and FEV_1 of 0.93 ± 0.1 L (33.7 ± 4.5% predicted). These values are significantly lower than those observed in patients not on supplemental oxygen or patients who used oxygen only during physical activities.

Relationship between $\dot{V}O_2$max and Severity of Disease

Data for the four severity groups, divided according to CT scan grades and continuous use of supplemental oxygen, are shown in Table 3. It can be seen that as the severity of disease increases, $\dot{V}O_2$max decreases. Other exercise parameters such as oxygen pulse and work rate are also progressively reduced, whereas ventilatory equivalent for CO_2 increases with disease severity. The proportion of patients who had reduced $\dot{V}O_2$max increased from 55% in group 1 to 88% in group 2, 93% in group 3, and 100% in group 4. Finally, the number of patients experiencing exercise-induced hypoxemia increased from 11 (11%) in groups 1 to 16 (40%) in group 2, and 32 (70%) in group 3. Despite use of supplemental oxygen during exercise testing, seven (23%) group 4 patients developed exercise-induced hypoxemia.

Relationship between $\dot{V}O_2$max and Histologic Severity of Disease

Of the 102 patients who underwent open lung biopsy, 18 and 12 patients, respectively, with LHSs of 1 and 2, had had lung biopsies within the year before CPET. We found that $\dot{V}O_2$max in patients with an LHS of 2 (991 ± 95 ml/min, 58.6 ± 5.2% predicted) was significantly lower ($p = 0.005$) than that in patients with an LHS score of 1 (1,359 ± 105 ml/min, 80.0 ± 4.6% predicted). In addition, D_{LCO} was significantly lower ($p = 0.043$) in patients with an LHS score of 2 (15.2 ± 1.7 ml/min/mmHg, 71.3 ± 7.0% predicted) than in patients with an LHS score of 1 (19.6 ± 1.2 ml/min/mmHg, 91.9 ± 5.1% predicted). There was no significant difference ($p = 0.183$) in FEV_1 between patients with an LHS score of 1 (2.25 ± 0.17 L, 80.8 ± 4.7% predicted) and patients with an LHS score of 2 (2.02 ± 0.22 L, 76.0 ± 8.5% predicted).

TABLE 3. LUNG FUNCTION AND EXERCISE PHYSIOLOGY IN FOUR GROUPS OF PATIENTS WITH LYMPHANGIOLEIOMYOMATOSIS CLASSIFIED BY GRADE OF SEVERITY OF COMPUTED TOMOGRAPHY SCANS AND USE OF OXYGEN

	1	2	3	4
Patients, n	100	40	46	31
Age	42.2 ± 0.8	47.0 ± 1.4*	45.6 ± 1.2	50.9 ± 1.5*
FEV_1, %	93.1 ± 1.6	69.9 ± 3.5*	65.2 ± 3.1*	41.7 ± 2.6‡
DL_{CO}, %	94.6 ± 1.8	0.2 ± 2.3*	55.1 ± 1.7†	37.1 ± 1.6‡
DL_{CO}/VA, %	112.6 ± 2.0	86.8 ± 2.6*	64.7 ± 1.8†	48.8 ± 2.2‡
Work rate, %	106.7 ± 2.7	87.5 ± 3.8*	72.8 ± 4.0*	58.5 ± 3.6‡
HR, %	91.5 ± 0.8	87.7 ± 1.5	83.5 ± 1.5*	75.9 ± 1.7†
$\dot{V}O_2$/HR, %	92.8 ± 2.1	76.0 ± 3.1*	68.2 ± 3.0*	63.7 ± 3.5†
$\dot{V}O_2$max	1,453 ± 36	1,116 ± 54*	948 ± 48*	768 ± 46‡
$\dot{V}O_2$max, %	84.7 ± 2.0	69.4 ± 2.7*	59.5 ± 2.8†	49.8 ± 2.7‡
$\dot{V}E$	61.1 ± 1.4	51.5 ± 2.4	45.5 ± 2.6*	32.7 ± 2.2‡
BR	38.0 ± 1.6	25.6 ± 3.0*	26.3 ± 3.2*	20.1 ± 2.8*
$\dot{V}E/\dot{V}CO_2$-AT	33.8 ± 0.6	40.6 ± 1.1*	44.7 ± 1.2*	47.3 ± 2.6†
RER-AT	0.99 ± 0.003	0.99 ± 0.003	1.0 ± 0.004	0.99 ± 0.005
Pa_{O_2}, rest	89 ± 1‡	81 ± 2‡	75 ± 2‡	63 ± 2‡
Sa_{O_2}, rest	97.9 ± 0.1	96.9 ± 0.2	95.5 ± 0.4	98.9 ± 0.2
Sa_{O_2}, exercise	96.5 ± 0.2	93.6 ± 0.5	90.3 ± 0.5‡	97.3 ± 0.5
ΔSa_{O_2}	−1.4 ± 0.2	−3.3 ± 0.4	−5.2 ± 0.4‡	−1.6 ± 0.4

Definition of abbreviations: BR = breathing reserve (%); DL_{CO} = diffusion capacity for carbon monoxide (ml/minute/mm Hg); DL_{CO}/VA = ratio of DL_{CO} to alveolar volume (ml/minute/mm Hg/L); HR = heart rate; RER-AT = respiratory equivalent ratio at anaerobic threshold; $\dot{V}E/VCO_2$-AT = ventilatory equivalent for CO_2 at AT; $\dot{V}O_2$max = maximal oxygen uptake (ml/min); ΔSa_{O_2} = change in Sa_{O_2} with exercise (%).

Group 1 = CT scan grade 1; group 2 = CT scan grade 2; group 3 = CT scan grade 3 and not on oxygen; group 4 = CT scan grade 3 on continuous oxygen therapy. Group 4 patients were exercised on supplemental oxygen. Data are means ± SEM.

* Significantly different from group 1.

† Significantly different from groups 1 and 2.

‡ Significantly different from the other three groups (analysis of variance).

Predictors of $\dot{V}O_2$max

We found that of all the independent variables that were statistically significant at the 0.1 level in the univariate analysis (Table 4), only DL_{CO} and FEV_1 were statistically significant predictors of $\dot{V}O_2$max ($p < 0.0001$ for both). However, the resulting $r^2 = 0.50$ indicated that these two lung function tests explain only one half of the $\dot{V}O_2$max variation, and inclusion of other variables did not increase the model accuracy. The correlation (r) between the $\dot{V}O_2$max and DL_{CO} tended to increase with disease severity score (0.35, 0.53, 0.69, 0.52 for severity scores 1, 2, 3, and 4, respectively). Similarly, the correlation of $\dot{V}O_2$max and FEV_1 increased with disease severity (0.27, 0.40, 0.52, 0.69 for severity scores 1, 2, 3, and 4, respectively). The correlation of DL_{CO} with $\dot{V}O_2$max is higher than that of FEV_1 for the first three severity scores but lower in the most severe group. It is possible that the administration of supplemental oxygen to group 4 patients improved exercise capacity and altered the correlation between $\dot{V}O_2$max and DL_{CO}, thus explaining why $\dot{V}O_2$max of patients exercised on supplemental oxygen became greater than expected for the degree of impairment in DL_{CO}.

TABLE 4. CORRELATION OF CLINICAL, ROENTGENOGRAPHIC, AND LUNG FUNCTION VARIABLES WITH $\dot{V}O_2$max IN 217 PATIENTS WITH LYMPHANGIOLEIOMYOMATOSIS

Variables	Correlation (r)	p Value
Length of disease	−0.096	0.1569
Use of oxygen	−0.377	< 0.0001
CT scan grade	−0.559	< 0.0001
FEV_1	0.619	< 0.0001
FEV_1/FVC	0.494	< 0.0001
RV	−0.341	< 0.0001
RV/TLC	−0.470	< 0.0001
DL_{CO}	0.674	< 0.0001
DL_{CO}/VA	0.557	< 0.0001
Pa_{O_2}, rest	0.499	< 0.0001

Definition of abbreviations: CT = computed tomography; DL_{CO} = diffusion capacity for carbon monoxide (ml/minute/mm Hg); DL_{CO}/VA = ratio of DL_{CO} to alveolar volume (ml/minute/mm Hg/L); RV/TLC = ratio between RV and TLC (percentage).

The p values were derived using a two-sided t test (for testing no association between variables).

DISCUSSION

In this study, which was conducted in a large population of patients with LAM, we found a high prevalence of abnormal exercise responses, suggesting the presence of gas exchange abnormalities, abnormal cardiovascular function, ventilatory abnormalities, and muscle fatigue. These heterogeneous abnormalities caused a decrease in exercise capacity in three fourths of the patients. A multivariate regression analysis showed that the only significant predictors of $\dot{V}O_2$max were DL_{CO} and FEV_1. Of note, exercise-induced hypoxemia occurred even in patients with seemingly mild compromise of lung function, with DL_{CO} being the best predictor of exercise-induced hypoxemia.

Pulmonary diseases can result in multiple abnormalities of both ventilatory, gas exchange, and cardiovascular responses to exercise (5, 17). Consistent with the clinical and functional heterogeneity of LAM, no single, unique pattern of response was observed in our patients. In some patients, there appeared to be a predominance of gas exchange abnormalities characterized by hypoxemia and/or an excessive ventilatory response to exercise. In others, low $\dot{V}O_2$ at AT, or failure to reach anaerobic threshold in the absence of ventilatory limitation, was observed. In a third group of patients, ventilatory abnormalities were a major component of exercise limitation (18). Finally, decreased exercise capacity without evidence of cardiorespiratory abnormalities was observed in some patients. The relative contributions of these factors into limiting exercise capacity varied from patient to patient in a manner that was not completely accounted for by their lung function, that is, D_{LCO}, FEV_1. This probably explains the wide variance in $\dot{V}O_2$max. Our study, however, does not allow for specific identification of all the pathophysiologic processes involved in causing low exercise capacity in LAM.

The close correlation of $\dot{V}O_2$max with D_{LCO} and FEV_1 and between the decline in Sa_{O_2} and D_{LCO} may suggest that CPET is of no more value than standard pulmonary function tests in assessing the severity of disease in LAM. $\dot{V}O_2$max, however, cannot be fully explained by D_{LCO} and FEV_1, and exercise-induced hypoxemia occurred in the presence of near normal D_{LCO} and FEV_1, suggesting that in LAM, lung function tests do not consistently predict gas exchange abnormalities during exercise. Although correlating well with D_{LCO} and FEV_1, as previously reported (15, 19), CT scan grades of severity also appeared not to be good predictors of gas exchange abnormalities in LAM. Indeed, despite having the same CT scan grade as severity score group 3, severity group 4 patients were on continuous oxygen therapy and had significantly lower $\dot{V}O_2$max and resting Pa_{O_2}. This finding is of importance because the prevalence and severity of exercise-induced hypoxemia in patients with LAM are probably even greater than those observed in our study. Indeed, the stipulated criterion of a decline in Sa_{O_2} of 4% or more is too stringent, and the most severely affected patients were tested on supplemental oxygen.

There was a close association between $\dot{V}O_2$max and LHSs. Patients with more severe scores had significantly lower $\dot{V}O_2$max. In addition, and as shown previously (4), D_{LCO} more closely followed LHSs than did FEV_1. Because LHSs are a predictor of death and time to transplantation (16), $\dot{V}O_2$max may also be a predictor of survival in patients with LAM. Long-term studies, however, will be required to determine whether $\dot{V}O_2$max is of value in predicting survival and time to transplantation.

In conclusion, the occurrence of exercise-induced hypoxemia in patients with mild degrees of impairment in lung function makes CPET an important measure of disease severity in LAM. This finding has both therapeutic, that is, treatment with oxygen, and prognostic implications. Measurement of D_{LCO} provides some general guidance regarding need for oxygen therapy, but exercise testing should be performed to determine the severity of gas exchange abnormality and supplemental oxygen requirements for the patients' level of physical activity.

CPET may also be of value in evaluating patients for referral to a lung transplantation center. $\dot{V}O_2$max was correlated with use of supplemental oxygen and was lowest in patients who subsequently underwent lung transplantation. Based on our pretransplant data and the fact that the waiting time on a transplantation list can be several years, patients with $\dot{V}O_2$max below 50% predicted and D_{LCO} under 40% predicted should probably be considered for referral to a lung transplantation center.

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